response. Genomic technologies can identify molecular subgroups with distinct genomic signatures. We investigated the genomic changes in patients with AML undergoing HCT using DNA microarrays. We analyzed 11 patients before HCT and at relapse after HCT, 6 patients had a normal karyotype at diagnosis and 5 had abnormal karyotype with different types of aberrations. After high resolution of whole genome DNA profiling analysis 5 of the 6 patients with normal karyotype showed genomic aberrations (GA) in the form of gains and losses (5/5 gains/losses) in several regions of different chromosomes with a median of 2 GA per case. The abnormal karyotype group, in addition to the cytogenetically detected aberrations GA were present in 2 out of 5 patients (5/4 gains/losses). Overall 64% of the patients had GA, not detected by conventional cytogenetics. All FAB subtypes of AML showed GA, being M5 and secondary AML both with more numerous GA (average: 12 and 17 GA respectively). At relapse 6 patients increased the number of GA, (median of 7 GA per case), while 3 patients presented a reduced number of GA (median 2 GA per case). The remaining 2 patients showed no additional changes. Before transplantation 16 chromosomes showed GA with a median of 3 GA per chromosome, average size of gains and losses were 1568 and 8046 kb respectively. At relapse 19 chromosomes had GA with a median of 4 GA per chromosome, average size of gains and losses were 697 and 8011 kb respectively. Chromosomes 11, 14 and 21 showed no GA at any time point. Our preliminary data demonstrate that AML is a genomically heterogeneous disease with a high incidence of small non recurrent DNA GA that can be detected even in cases with normal karyotype. Cryptic genomic changes are likely to play a role in relapse after allogeneic transplantation.

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CLADRIBINE (2CDA) IS COMPARABLE TO FLUDARABINE IN A BUSULFAN-BASED REDUCED- INTENSITY REGIMEN

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Reduced-intensity stem cell transplantation (RIST) with a purine analog most often involves fludarabine (Flu). The alternative drug, 2CdA, is rarely used partly because of a potential risk of renal toxicity. We retrospectively reviewed the medical records of 282 patients (median age, 54 y; range, 21-68) with various hematological malignancies who underwent RIST between 1999 and 2007 with a conditioning regimen that consisted of busulfan (po 8 mg/kg or iv 6.4 mg/kg) in combination with either 2CdA (0.66 mg/kg, n = 71, C-group) or Flu (180 mg/m^2, n = 211, F-group). Seventy-four patients also received 2-4 Gy of TBI. The donor was related (BM 8, PB 177) in 185 patients, and unrelated in 97 (BM 79, PB 1, CB 17). GVHD prophylaxis consisted of cyclosporine (CSP, starting dose 3 mg/kg/day civ, target whole blood conc. 250-350 ng/ml, n = 232) or tacrolimus (starting dose 0.03 mg/kg/day civ, target whole blood conc. 10-20 ng/ml, n = 50), with (n = 131) or without (n = 151) MTX. Sixty-nine patients also received anti-human T- lymphocyte immunoglobulin (ATG, 5-10 mg/kg). Except for the stem cell sources, there were no significant differences between the C- and F-groups. Acute renal failure (ARF) within 100 days was defined as there was a greater than two-fold rise in the serum creatinine concentration compared to the baseline. The median follow-up in surviving patients was 1589 days (50-3291). The 275 patients who survived more than 30 days (except for one patient who died of relapse) all achieved neutrophil engraftment in a median 13 days (range, 5-42 days). No significant difference was observed between C- and F-group with regard to OS (59% vs 48% at 3 y, p = 0.20), relapse rate (42% vs 35% at 3 y, p = 0.42), NRM (7% vs 6% on d100, 22% vs 32% at 3 y, p = 0.15), or the cumulative incidences of ARF (34% vs 27% on d 100, p = 0.26), grade II-IV acute GVHD (46% vs 47%, p = 0.40), and extensive chronic GVHD (62% vs 54% at 3 y, p = 0.21). Multivariate analyses showed that TBI [HR 2.96 (1.86-4.72), p < 0.001] for NRM, TBI [HR 1.75 (1.23-2.49), p = 0.002] and high-risk disease [HR 2.39 (1.62-3.55), p < 0.001] for OS, and TBI [HR 1.98 (1.25-3.14), p = 0.004] and CSP [HR 2.10 (1.06-4.17), p = 0.03] for ARF were significant factors for poor outcomes. However, 2CdA was not significantly associated with NRM, OS or ARF. Our study suggested that a relatively low dose of 2CdA was tolerable and feasible as part of a reduced-intensity regimen, and was not associated with any significant nephrotoxicities.

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TANDEM AUTO-ALLO IN ACUTE MYELOID LEUKEMIA (AML) PATIENTS IN FIRST COMPLETE REMISSION (CR)

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Background: High and intermediate risk AML can benefit from allo-SCT in first CR. Reduced intensity conditionings (ALLO-RIC) decreases toxicity. However there are now data in favour of lower disease control as compared with standard CDT. We hypothesized that if a better quality of remission could be achieved, the relapse incidence could be lowered.
Patients and methods: From 2001 to 2008, 31 AML patients in first CR received a tandem auto-allo program. At diagnosis, median number of WBC was 3 × 10e9/l (0.9-235), 13% of patients have extramedullary localisations. 64% of patients were considered at high-risk (cytogenetic, secondary disease or double inductions) and 36% at intermediate risk. After reaching CR1, all but two patients received a consolidation course with high-dose cytarabine (HD-ARAC, 24 g/m^2 in 93%) CT, followed by autologous stem cell harvest. HD melphalan (HD-PAM 140 mg/m^2) was followed by autologous stem cells reinfusion. Then, ALLO-RIC consisted of fludarabine (90 mg/m^2) plus (2 Gy) TBI (3 pts) or fludarabine (150 mg/m^2), busulfan over 2 days, and thymoglobuline (2.5 or 5 mg/kg). GVHD prophylaxis was CyA. 3 patients received also mycofenolate mofetil. All donors, but one, were HLA identical sibling. The median number of allo CD34+ cells was 6.1 × 10e6/Kg. Prognostic scores (HCT-CI, PAM, EBMT) were retrospectively calculated for each patient. All pts have a performance status ≥ 90%.
Results: Median fup from diagnosis and ALLO-RIC were 40 and 34 months, respectively. Median days between last CT and HD-PAM was 51 (30-77) and between HD-PAM and ALLO-RIC was 69 (55-176). 5 pts relapsed for a 4 year CI of 15% (3-29). At last fup, 13 have died (relapse: 5; toxicity: 8). Grade II-IV aGVHD and cGVHD CI were respectively 26% and 65% (extensive 84%). GVHD was the cause of death in seven pts. Six pts (19%) reactived CMV, and 1 pt did not survive to an interstitial pneumonitis. The 4-year overall survival (OS), relapse free survival (RFS), and 1-year TRM were 61% (43-76), 59% (41-75), and 16% (3-29), respectively. In multivariate analysis, prognostic scores did not influence TRM and OS.
Conclusions: This report showed that i) tandem auto-allo is feasible in AML pts; ii) acute GVHD incidence is not increased; iii) prognostic scores did not impact on TRM and survival; iv) TRM is low with GVHD as main cause of death; v) low relapse rate is documented and invites further development.

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LONG TERM OUTCOMES OF ALLOGENEIC STEM CELL TRANSPLANTATION FOR CHRONIC LYMPHOCYTIC LEUKEMIA

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Introduction: Allogeneic Stem Cell Transplantation (Al-SCT) remains an option for patients with advanced Chronic Lymphocytic Leukemia (CLL) with high risk features.

Methods: We performed a retrospective analysis of our patients with CLL/Pro-lymphocytic leukemia (PLL) who underwent Al-SCT at our center between August 1989 and February 2009. The objective of this study is to evaluate the overall survival (OS), relapse free survival (RFS), acute and chronic graft versus host disease (aGVHD, cGVHD). We also compared the intensity of conditioning regimens (conventional: CIC Vs reduced: RIC), donor type, (matched sibling: MSD vs matched unrelated: MUD), graft source (bone marrow: BM vs peripheral blood: PB) and their impact on OS, RFS, aGVHD and cGVHD.

Results: There are 59 patients available for review. Patients characteristics are listed in table 1. There were a variety of conditioning regimens; for the CIC, 36 pts. received Busulfan based regimens and 10 pts. Total Body Irradiation based regimens, for the RIC 13 pts. received different fludarabine based regimens. Donor types were 48 MSD and 11 MUD. Source was BM in 27 and PB in 32 pts. Most (43/59 pts) received CyA-MTX as the GvHD prophylaxis but 12 and 4 pts. received Mycophenolate and Campath with CyA respectively. The median follow up is 45 months (7-237). The median survival time is 115 months with a 5 year survival probability of 57% (95% CI: 0.43-0.68). OS was not statistically significantly different when comparing type of conditioning or graft source, however a significant improvement in OS with MSD type over MUD, (P value = 0.0007). The 3-year RFS is 48% (95% CI: 0.35-0.60) with no statistically significant difference according to regimen intensity and graft source, with a significant superior outcome for MSD Vs MUD (P value = 0.002). Grade 2-4 aGvHD was seen in 40 cases. The cumulative rates of aGvHD 2-4 are not different between the conditioning, donor type and graft source. Forty-one cases (68%) experienced cGvHD (18% limited,50% extensive) with no difference according to regimen intensity and donor type, although a significantly increased incidence in the PB group (P value = 0.03). Causes of death include infection (40%), GVHD (33%), relapse (18%) and VOD (9%).

Conclusions: Acceptable survival post Al-SCT is possible in CLL although TRM is significant. This retrospective analysis demonstrates inferior survival for MUD recipients and similar outcomes when comparing RIC and CIC regimens.

Table 1. Patients characteristics

Pts studied , n.	59
Diagnosis : CLL / PLL	54 / 5
Mean age (range), y	46 (27-67)
Gender (F /M), n.	19 / 40
Number of prior regimens, mean (range)	4 (1-9)
Prior Purine analogue	84 %
Prior Rituximab	11 %

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OUTCOME OF HEMATOPOIETIC STEM CELL TRANSPLANTATION FOR CHILDREN WITH SEVERE APLASTIC ANEMIA. TEN YEARS EXPERIENCE IN A LARGE PEDIATRIC TRANSPLANT CENTRE

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Severe aplastic anemia (SAA) in children is a rare and serious disease. The best potential cure is allogeneic hematopoietic stem cell transplantation (SCT). Our objective herein was to review the outcome of all children who received SCT for a diagnosis of SAA between 1998-2008 in the Hospital for Sick Children, Toronto. Fifty-eight children were included in the study. Median age at SCT was 10.1 years (range 1.6-17 yrs). Median time from diagnosis to SCT was 8.8 months (range 1-142 months). Stem cell source was related in 38; living unrelated in 18 and 2 patients received cord progenitor stem cells.

Twenty-seven patients received immunosuppressant therapy prior to SCT. Conditioning regimen for the related donors included cyclophosphamide and antithymocyte globulin (ATG). For the unrelated, either a single dose total body irradiation (TBI) 200 cGy or fludarabine was added. Overall survival for the whole group was 84%. In a univaraite analysis, factors affecting survival were: stem cell source (related 90%; unrelated 71%); type of SAA (idiopathic 90%; post hepatitis or drug related 70%; possible hereditary 60%); previous immunossupressive therapy and multiple transfusions (of 10 patients who died, 8 were treated with 1 or 2 courses of immunossupressive therapy and 6 of them had more than 20 blood transfusions before SCT).

Incidence of acute and chronic graft-versus host disease (GVHD) were 29% and 14% respectively with 6 out of 8 patients with chronic GVHD were recipient of unrelated donors. Ten patients died due to transplant related mortality (TRM) and seven were recipient of unrelated donors. Causes of death were: sepsis, severe VOD, CMV infection and multiorgan failure.

Long term chimerism testing showed 54% of the patients continued to have full donor status, 22% are stable mixed chimerism and 4% with decreased chimerism; 15% suffered engraftment failure (5%-primary and 10%-secondary) and 5% of patients died before engraftment and were not evaluable for engraftment. Of the 9 patients with primary and secondary graft failure 6 had unrelated donor.

In conclusion: Our results suggest that factors affecting prognosis of children with SAA treated with SCT are: etiology of SAA, previous immunosuppressant therapy, multiple transfusions and type of donor. Furthermore, engraftment failure continues to be a problem in particular for recipient of unrelated donors.

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RELATION OF TNFA, TNFB AND TNFRII GENE POLYMORPHISMS TO OUTCOMES AFTER UNRELATED HAEMATOPOIETIC CELL TRANSPLANTATION WITHIN CHINESE POPULATION

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Background: The genes code TNFα (TNFA), TNFβ (TNFB) and TNF receptor II (TNFRII) contain multiple single nucleotide polymorphisms (SNPs). The present study was designed to test association of these genes polymorphisms with outcomes after unrelated HSCT within Chinese population.

Methods: A total of 138 pairs of donors and recipients, who had undergone HSCT from 2001 to 2009 at our center, were tested for TNFA-1031(T > C), -863(C > A), -857(C > T), -238(G > A), TNFB + 252(A > G) and TNFRII codon 196 (T > G) genotypes.

Results: (1) Recipients and/or donors with TNFA-857 C/C genotype or TNFB + 252 G allele-positive had a higher incidence of aGVHD ($P < 0.05$). TNFRII 196 T/T genotype in donors side or recipients side showed a stronger trend toward development of aGVHD (in donor side: $P = 0.028$; in recipient side: $P = 0.086$). When these effects were analyzed only in 96 pairs of HLA matched cases, donor and/or recipient TNFA-857 and TNFB + 252 genotype also affected aGVHD incidence. The influence of TNFRII genotype was not significant except the recipient type showed a trend ($P = 0.074$).The genotypes of TNFA -1031, -863 and -238 were not found to be associated with the risk of aGVHD. (2) TNFA-857, TNFB + 252 and TNFRII 196 polymorphic features, together with other factors were subjected to multivariate analysis for aGVHD. Myeloablative conditioning(RR = 3.771, $P = 0.004$), donor with TNFA-857C/C genotype (RR = 2.29, $P = 0.006$) and recipient with TNFB + 252 G allele-positive (RR = 1.789, $P = 0.036$) were found to significantly contribute to the development of aGVHD. Donor-recipient gender was found to be a less significant factor ($P = 0.079$). As to grade II-IV aGVHD, myeloablative conditioning (RR = 3.929, $P = 0.022$), HLA mismatching (RR = 1.691, $P = 0.048$) and donor with TNFA-857 C/C genotype (RR = 3.748, $P = 0.002$) were found to